PLATFORMS, IN PARTICULAR PROSTHESES, WITH BIOLOGICALLY ACTIVE COATINGS

The subject of the invention is the use of biologically active compounds for the coating of platforms, in particular prostheses. It relates in particular to the coating of stents comprising a biologically active coating.

It is known that the treatment of stenoses of the coronary arteries was revolutionized by coronary angioplasty, which consists of opening the stenosis with a balloon. This technique was improved by using a metal arterial endoprosthesis, called a "stent", in order to prevent retractile cicatrization of the artery causing restenosis, i.e. the reappearance of the stenosis. However, in a good number of cases, varying from 20 to 40% depending on the type of lesion, it was found that the insertion of a stent in an artery causes a restenosis linked with a neointimal hyperplasia, which results both from an excess of scar tissue and from a reaction to the foreign body. In order to overcome these problems, it was proposed to coat the stents with medicated substances capable of combating restenoses.

Of the strategies proposed, that which consists of using molecules with cytotoxic or cytostatic effects aroused much interest. During the first 6 months of insertion of stents with a coating of cytotoxic or cytostatic compounds, no restenosis was observed.

However, these molecules have the drawback of also inhibiting the scarring phase, which produces a risk of late thrombosis on a bare metal body, as well as the creation of a space between the stent and the artery wall by dilatation of this wall (hereafter called positive remodelling).

On animal models, a late restenosis phenomenon was also observed.

It therefore transpires that, although the use of stents as pharmacological platforms allowing delivery of a medicament constitutes a beneficial approach, the therapeutic families proposed up until now are not satisfactory.

The inventors found that, by following another medication-based approach, based on the use of multi-functional compounds, it was possible to have a regulatory effect on the extracellular matrix, and to inhibit the scar tissue responsible for hyperplasia, thus preventing intra-stent restenosis. This result proved to be applicable generally to the coating of other prostheses in other medical indications, and in general to any biological platform.

The invention is therefore based on a multiple-effect strategy aimed at cell proliferation and migration, the metabolism of the extracellular matrix and control of inflammation.

The aim of the invention is therefore to use novel compounds in the development of coatings for platforms, in particular prostheses.

It also relates, as new products, to these platforms and prostheses, in particular stents having such coatings.

The use according to the invention is characterized by the use of multi-functional compounds to develop a pharmacologically active coating on a platform/prosthesis.

Surprisingly, such coatings make it possible, in a situation of mechanical trauma of the tissues causing an inflammatory response, to avert arterial restenosis.

Unlike the prior art strategies mentioned above, such regulators do not affect the cell cycle and therefore do not have a deleterious effect on the endothelium which may result in the appearance of late thromboses, a positive remodelling or a late restenosis.

It is thus possible to keep a healthy wall which is not adversely affected by the loss of or damage to cells, which also allows thrombosis phenomena to be averted.

Preferably, decorin and/or a peptide fragment of decorin, or the derivatives of decorin and/or of a fragment of decorin, possessing the properties of these compounds but chemically modified in order to give them advantageous properties for a given application, are used.

Human decorin is a protein comprising 359 amino acids with a chain of glycosaminoglycans, with a molecular weight of 100 to 120 kDa. It corresponds to the following sequence:

mkatiillll aqvswagpfq qrglfdfmle deasgigpev pddrdfepsl gpvcpfrcqc hlrvvqcsdl gldkvpkdlp pdttlldlqn nkiteikdgd fknlknlhal ilvnnkiskv spgaftplvk lerlylsknq lkelpekmpk tlqelrahen eitkvrkvtf nglnqmivie lgtnplkssg iengafqgmk klsyiriadt nitsipqglp psltelhldg nkisrvdaas lkglnnlakl glsfnsisav dngslantph lrelhldnnk ltrvpgglae hkyiqvvylh nnnisvvgss dfcppghntk kasysgvslf snpvqyweiq pstfrcvyvr saiqlgnyk

The decorin used according to the invention advantageously corresponds to the following domains:

- Domain I: Signal peptide + propeptide,
- Domain II: Cysteine residues + glycosaminoglycans (GAGs) attachment site
- Domain III: Leucine-rich repeats (LRR), protein core (38-43 kDa),
- Domain IV: Cysteine residues with loop.

The active protein fragment alternatively proposed is defined as follows: bioactive decorin fragment between the amino acid in positions (115) and (260), 15-20 kDa.

The presence of these compounds on a platform allows their multi-functional properties to be exploited. It is thus possible to act on cell proliferation (by inhibiting the action of PDGF and of EGF, by binding on the EGF receptor), on cell migration (by inhibiting migration by action on fibronectin and thrombospondin, and by inhibiting degradation of the extracellular matrix), on inflammation (by reducing the infiltration of macrophages; by inhibiting the inflammatory action of interleukin 1 and the inflammatory response to angioplasty trauma on the smooth muscular cells by maintaining their contractile phenotype (which does not secrete extracellular matrix and pro-inflammatory cytokines)), and by acting against fibrosis (by inhibiting the accumulation of the extracellular matrix, in particular via its action on interleukin 1, TGFβ-1 and PDGF BB).

According to another feature, the invention also relates, as novel products, to platforms and prostheses, characterized in that they comprise a coating containing a therapeutically effective quantity of at least one compound as defined above.

By therapeutically effective quantity is meant a quantity which allows the effects mentioned above to be obtained, especially regulation, in particular the inhibition of the surplus of extracellular matrix produced in response to the trauma of the inserted platform or prosthesis. Quantities of the order of 10 to 100 $\mu g/mm^2$ proved to be appropriate.

Preferred platforms and prostheses more particularly contain a therapeutically effective quantity of decorin and/or of a peptide fragment of decorin, and/or of a derivative of decorin or of a fragment of decorin.

These compounds are bound directly to the platform or prosthesis, or via a biostable or biodegradable coating such as a lactic acid polymer. The binding of the compounds can be reversible or irreversible. The platforms or prostheses can be biodegradable, for example made of lactic acid polymer. They can be also made of

manganese. The release can either not take place, or take place at a speed which depends on the coating, the binding used, the platform (degradable or not).

The prostheses which are more specifically concerned correspond to implantable devices or endoluminal prostheses, in particular endovascular, urological, respiratory or digestive prostheses.

The antifibrotic effect of decorin and of a fragment of decorin is advantageously also exploited with prostheses outside arterial application, in particular in urological, digestive, bronchopulmonary applications.

In these applications, the compounds used are bound to a platform which is for example made of metal, or is bioresorbable. This binding can be temporary or permanent. The compound then acts in the proximity of the platform, this zone being at the source of the triggering of the greatest inflammation and therefore of the cell proliferation and migration, and the extracellular matrix accumulation.

Other characteristics and advantages of the invention are given in the following examples.

Production of stents with a bioactive coating of decorin and arterial application

Operating according to standard techniques, a biostable or biodegradable coating based on polymers, for example a lactic acid polymer, containing a pharmacologically active quantity of decorin, allowing the release of active ingredient over 30 days, is applied to a metal stent for example made of 316L steel.

In vivo, the decorin locally inhibits restenosis in the iliac artery of rabbits. After 2 months of observations, no restenosis phenomenon was observed.

By way of a variant, the decorin is bound directly to the stent without a coating.